APPENDIX A

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TRANSMITTAL SHEET

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DATE *10 October 2003*

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REMARKS:

Applicant:	Eisai Co. Ltd.
Intl. Appln. No.:	PCT/US02/40744
Intl. Filing Date:	18 December 2002
Priority:	U.S.S.N. 60/343,678 filed 28 December 2001
For:	LUMINACIN ANALOGS AND USES THEREOF

Please see the attached response to the Written Opinion dated 11 August 2003.

TIME SENT: _____ *OPERATOR:* _____ *CLIENT NO.* **2003946-0022**

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1 PCT/US02/40744	2003946-0022	Response to Written Opinion (4 pp.)
2		Request for Amendment (3 pp.)
3		Appendix A (9 pp.)
4		Substitute sheets (10 pp.)
5		RReceipt for subsequently
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7		Fax Cover (1 p.)
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Eingereichte Unterlagen Anmeldungs- (und Direktions-*) Nr./Patent Nr. Application (and Directorate*) No./Patent No. N° de la demande (et de la direction*)/n° du brevet		Items filed Ihr Zeichen Your reference Votre référence	Pièces envoyées ggfs. Art und Datum der Unterlagen** Nature and date of items (optional)** Nature et date des pièces (facultatif)**
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ATTORNEY DOCKET NUMBER: 2003946-0022 (VD 1207/PCT)

IN THE EUROPEAN PATENT OFFICE
AS INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Applicant:	Eisai Co. Ltd.
Intl. Appln. No.:	PCT/US02/40744
Intl. Filing Date:	18 December 2002
Priority:	U.S.S.N. 60/343,678 filed 28 December 2001
For:	LUMINACIN ANALOGS AND USES THEREOF

VIA FACSIMILE
011-49-89-2399-4465
CONFIRMATION BY
INTERNATIONAL COURIER

EUROPEAN PATENT OFFICE
D-80298 MUNICH
GERMANY
Authorized Officer: Examiner

Dear Sir/Madam:

RESPONSE TO WRITTEN OPINION

This paper is submitted in response to the Written Opinion mailed 11 August 2003, for the above-identified application. The deadline for response to the Written Opinion is 11 October 2003; Thus Applicant respectfully submits that the filing of this response on 10 October 2003 is timely. Responsive to the Written Opinion Applicant respectfully submits the following Remarks.

Applicant thanks the Examiner for his/her careful consideration of this case, and requests that he/she reconsider his/her evaluation of the ability of the claims to satisfy the International Standards of Patentability in light of this Response.

The Opinion is based on the documents cited on the International Search Report (ISR) issued 28 March 2003, in particular the documents cited "X". The ISR cites the following references in category X:

1. Naruse *et al.*, "Luminacins: a family of capillary tube formation inhibitors from streptomyces sp. I. Taxonomy, fermentation, isolation, physico-chemical properties and structure elucidation" *Journal of Antibiotics, Japan Antibiotics Research Association, Tokyo, JP*, 53(6):579-590, 2000;

2. Wakabayshi, *et al.*, " Luminacins: a family of capillary tube formation inhibitors from streptomyces sp. II. Biological activities", *Journal of Antibiotics, Japan Antibiotics Research Association, Tokyo, JP*, **53**(6):591-596, 2000;

3. Sharma, *et al.*, "UCS15A, a non-kinase inhibitor of Src signal transduction", *Oncogene, Basingstoke, Hants, GB*, **20**(17): 2068-2079, 2001; and

4. Tatsuta, *et al.*, "The first total synthesis and establishment of absolute structure of luminacins C1 and C2", *Tetrahedron Letters*, **42**(43), 7625-7628, 2001.

As detailed in the Request for Amendment under PCT Article 34 filed herewith, claims 1, 22 and 43, as amended, include the proviso that "*when R_4, R_5, R_8 and R_{10} are each hydroxyl, R_{13} and R_{14} are each methyl, R_2 and R_3, taken together, form an epoxide, R_7 is hydrogen and n is 1, the following groups do not occur simultaneously as defined:*

(i) R_1 is methyl, R_9 is hydrogen, (R_{11}, R_{12}) is (=O) and R_6 is ethyl or isopropyl;

(ii) R_1 is methyl, R_9 is CHO, (R_{11}, R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;

(iii) R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;

(iv) R_1 is methyl, R_9 is $COCH_3$, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and

(v) R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl"

Therefore, claims 1, 22 and 43 specifically exclude:

Luminacins A_1, A_2, B_1, B_2	[proviso (i)]
Luminacins C_1, C_2, E_1, E_2, E_3	[proviso (ii)]
Luminacins D, G_1, G_2	[proviso (iii)]
Luminacin H	[proviso (iv)]
Luminacin F	[proviso (i)]

Reference 1 (Naruse *et al.*) discloses Luminacins A_1, A_2, B_1, B_2, C_1, C_2, D, E_1, E_2, E_3, F, G_1, G_2 and H. As mentioned above, these luminacins are specifically excluded from the claimed invention. In addition, Reference 1 does not teach nor suggest any other luminacin analogs (*e.g.*, synthetic analogs), nor does it teach pharmaceutical compositions comprising luminacin analogs or a method of using them to treat cancer. Therefore, Reference 1 cannot

anticipate nor render obvious the presently claimed invention.

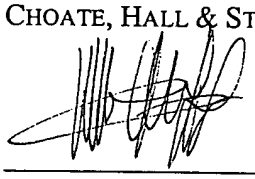
Reference 2 (Wakabayashi *et al.*) reports biological studies concerning naturally occurring luminacins. For example, Table 1 page 593 reports IC_{50} values of Luminacins A_1, A_2, B_1, B_2, C_1, C_2, D, E_1, E_2, F, G_1 and H in assays for anti-angiogenesis and anti-proliferative activity. Again, these naturally-occurring luminacins are specifically excluded from the claimed invention. In addition, although Reference 2 teaches the anti-angiogenic activity of fourteen naturally occurring luminacins (*e.g.*, A_1 through H), it does not provide any teaching or guidance for any other luminacin analogs (*e.g.*, synthetic analogs), nor does it teach pharmaceutical compositions comprising luminacin analogs or a method of using them to treat cancer. Therefore, Reference 2 cannot anticipate or render obvious the presently claimed invention.

Reference 3 (Sharma *et al.*) reports Src-inhibitory effects of UCS15A by a mechanism that involves disruption of protein-protein interactions mediated by Src. According to Figure 1 on page 2070 of Reference 3, UCS15A is luminacin C_1 or C_2, which, as mentioned above, are specifically excluded from the invention, as claimed. In addition, Reference 3 does not teach nor suggest luminacin analogs other than luminacin C_1 and C_2 (*e.g.*, synthetic analogs), nor does it provide any suggestion or teaching for pharmaceutical compositions comprising such compounds or a method of using them to treat cancer. Therefore, Reference 3 cannot anticipate or render obvious the presently claimed invention.

Reference 4 (Tatsuta *et al.*) discloses luminacins C_1 and C_2 and synthetic intermediates thereof. As mentioned above, claims 1, 22 and 43 specifically exclude luminacin C_1 and C_2. In addition, claim 1 includes the proviso that "*when R_1 is methyl, R_2 and R_3, taken together, form an epoxide, R_6 is ethyl, R_7 is hydrogen, (R_{11}, R_{12}) is (OMe, H), R_{13} and R_{14} are each methyl and n is 1, the following groups do not occur simultaneously as defined: R_4 and R_5 is OH or OBn, R_8 and R_{10} is OH or $-OCH_2OCH_3$ and R_9 is –CHO, $-CH_2OH$ or $-CH_2OTBS$*" which specifically excludes the synthetic intermediates disclosed in Reference 4. Also, Reference 4 does not does not teach nor suggest luminacin analogs other than luminacin C_1 and C_2 (*e.g.*, synthetic analogs), nor does it provide any suggestion or teaching for pharmaceutical compositions comprising these compounds or a method of using them to treat cancer. Therefore, Reference 4 cannot anticipate or render obvious the presently claimed invention.

In light of the above Remarks, Applicant respectfully submits that all claims, as amended, meet the International Standards of Patentability. A favorable International Preliminary Examination Report is respectfully requested.

Respectfully Submitted,
CHOATE, HALL & STEWART



Dated: 10 October 2003

Nadège M. Lagneau, Ph.D.
Agent for Applicant

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IN THE EUROPEAN PATENT OFFICE
AS INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Applicant:	Eisai Co. Ltd.
Intl. Appln. No.:	PCT/US02/40744
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For: LUMINACIN ANALOGS AND USES THEREOF

VIA FACSIMILE
011-49-89-2399-4465
CONFIRMATION BY
INTERNATIONAL COURIER

EUROPEAN PATENT OFFICE
D-80298 MUNICH
GERMANY
Authorized Officer: Examiner

Dear Sir/Madam:

REQUEST FOR AMENDMENT UNDER PCT ARTICLE 34

1. Applicant respectfully requests authorization from the International Preliminary Examining Authority for amendment under PCT Article 34 and respectfully submits that the replacement sheets, as submitted herewith, reflect claim amendments which do not introduce new matter. Applicant submits herewith replacement sheets number 68, 69, 74-77 and 80-82, to replace sheets number 68, 69, 74-77 and 80-82, originally filed for this application.

2. In respect of each claim appearing in the international application based on replacement sheets 68, 69, 74-77 and 80-82 submitted herewith, and in accordance with PCT Section 205(b), the following claim(s) is/are:

(i) Unchanged: Claims 2, 20, 21, 40-42 and 45-46 are unchanged;

(ii) Replaced: Claims 1, 22-26 and 43 are replaced with new claims 1, 22-26 and 43, respectively;

(iii) Canceled: Claim 44 is canceled.

A marked-up copy of Claim Replacements highlighting the changes is provided herewith as attached Appendix A. Deletions are represented in strikethrough, and additions

are represented in underlining.

Applicant respectfully submits that no new matter is presented with these amendments. Specifically, claim 1, as amended, includes recitation of the variable R_7 in the proviso (*i.e.*, "R_7 is hydrogen" in proviso (a)), which sought to exclude the luminacins listed in the table bridging pages 1 and 2 of the specification, but was inadvertently omitted at the time of filing. In addition, claim 1, as amended, includes the proviso that "*when R_1 is methyl, R_2 and R_3, taken together, form an epoxide, R_6 is ethyl, R_7 is hydrogen, (R_{11}, R_{12}) is (OMe, H), R_{13} and R_{14} are each methyl and n is 1, the following groups do not occur simultaneously as defined: R_4 and R_5 is OH or OBn, R_8 and R_{10} is OH or $-OCH_2OCH_3$ and R_9 is $-CHO$, $-CH_2OH$ or $-CH_2OTBS$*" which specifically excludes the synthetic intermediates disclosed in the Tatsuta *et al.* reference cited in the Written Opinion (*i.e.*, Reference 4).

Claim 22 has been amended to include recitation of the variable R_7 in the proviso (*i.e.*, "R_7 is hydrogen"), which was inadvertently omitted at the time of filing.

Claims 23-26 have been amended to correct the structure by replacing "OR_5" with "R_5". Support for this amendment can be found *inter alia* in original claims 2-5 and 45-48 wheer the structures are correctly depicted. Additional support can be found, for example, in original claim 33 in the recitation that R_5 (*e.g.*, in the structures of claims 23-26) is hydroxyl or lower alkoxyl. Thus the oxygen atom is already taken into account in R_5 itself.

Claim 43, as amended, includes the proviso that "when R_4, R_5, R_8 and R_{10} are each hydroxyl, R_7 is hydrogen, R_{13} and R_{14} are each methyl, R_2 and R_3, taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

(i) R_1 is methyl, R_9 is hydrogen, (R_{11}, R_{12}) is (=O) and R_6 is ethyl or isopropyl;

(ii) R_1 is methyl, R_9 is CHO, (R_{11}, R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;

(iii) R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;

(iv) R_1 is methyl, R_9 is $COCH_3$, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and

(v) R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl". Support for this amendment can be found *inter alia* in original claim 44, now canceled.

Applicant submits that the amendments to the claims, as described above and detailed herein, do not present new matter. Thus Applicant respectfully requests entry of these amendments, and consideration of these amendments in processing the application.

3. The deletion of any claims and any other loss of claimed subject matter is being made

solely to expedite prosecution of the subject matter now claimed, rather than in acquiescence to any positions taken by the Examiner. In fact, Applicant is *not* acquiescing to any of those positions and is submitting the present amendments without prejudice to the subsequent prosecution of claims to some or all of the subject matter which might be lost by virtue of this paper. Applicant additionally reserves the right to re-introduce the subject matter of any of the canceled claims, or subject matter which might be lost by virtue of amendments set forth in this paper, in the application.

Applicant hereby requests that the ISA begin its examination upon this submission. Favorable action is respectfully requested.

Respectfully submitted,
CHOATE, HALL & STEWART

Dated 10 October 2003

Nadège M. Lagneau, Ph.D.
Agent for Applicant

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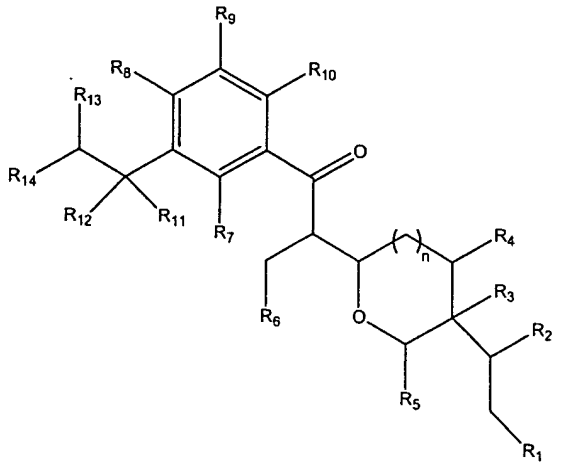
- APPENDIX A –

VERSION WITH MARKINGS TO SHOW CHANGES MADE

CLAIM REPLACEMENTS

1. A compound having the structure:



~~and~~ or pharnaceutically acceptable ~~derivatives~~ derivative thereof;

wherein n is 0, 1 or 2;

R_1 is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_2 and R_3 are each independently hydrogen, or, when taken together, may be –O- or –$(CH_2)_q$- , wherein q is 1, 2 or 3;

R_4 is hydrogen, hydroxyl, protected hydroxyl or OR^i, or an aliphatic or heteroaliphatic moiety,

wherein R^i is an aliphatic or heteroaliphatic moiety;

R_5 is hydrogen, hydroxyl, protected hydroxyl or OR^{ii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{ii} is an aliphatic or heteroaliphatic moiety, or wherein R_1 and R_5, when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R_6 is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_7 is hydrogen, hydroxyl, protected hydroxyl, OR^{iii}, or an aliphatic or heteroaliphatic

moiety,

wherein R^{iii} is an aliphatic or heteroaliphatic moiety;

R_8 is hydrogen, hydroxyl, protected hydroxyl or OR^{iv},

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R_9 is hydrogen, $-CF_3$, -CHO, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R_{10} is hydroxyl or protected hydroxyl;

R_{11} and R_{12} are each independently hydrogen, hydroxyl or OR^v, or an aliphatic or heteroaliphatic moiety, or, when taken together, may be –(C=O)-;

wherein R^v is an aliphatic or heteroaliphatic moiety;

and R_{13} and R_{14} are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or ~~unsubstitued~~ unsubstituted;

~~with the proviso that when R_4, R_5, R_8 and R_{10} are each hydroxyl, R_{13} and R_{14} are each methyl, R_2 and R_3, taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:~~

with the proviso that:

(a) when R_4, R_5, R_8 and R_{10} are each hydroxyl, R_7 is hydrogen, R_{13} and R_{14} are each methyl, R_2 and R_3, taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

(i) R_1 is methyl, R_9 is hydrogen, (R_{11}, R_{12}) is (=O) and R_6 is ethyl or isopropyl;

(ii) R_1 is methyl, R_9 is CHO, (R_{11}, R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;

(ii) R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;

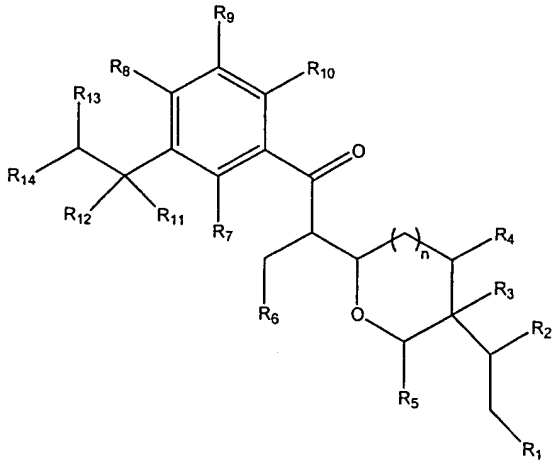
(iv) R_1 is methyl, R_9 is $COCH_3$, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and

(v) R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ~~ethyl.~~ ethyl; and

(b) when R_1 is methyl, R_2 and R_3, taken together, form an epoxide, R_6 is ethyl, R_7 is hydrogen, (R_{11}, R_{12}) is (OMe, H), R_{13} and R_{14} are each methyl and n is 1, the following groups do not occur simultaneously as defined: R_4 and R_5 is OH or OBn, R_8 and R_{10} is OH or $-OCH_2OCH_3$ and R_9 is –CHO, $-CH_2OH$ or $-CH_2OTBS$.

22. A pharmaceutical composition comprising:

a compound having the structure:



~~and~~ or pharmaceutically acceptable ~~derivatives~~ derivative thereof; and

a pharmaceutically acceptable carrier;

wherein n is 0, 1 or 2;

R_1 is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_2 and R_3 are each independently hydrogen, or, when taken together, may be –O- or $-(CH_2)_q-$, where q is 1, 2 or 3;

R_4 is hydrogen, hydroxyl, protected hydroxyl or OR^i, or an aliphatic or heteroaliphatic moiety,

wherein R^i is an aliphatic or heteroaliphatic moiety;

R_5 is hydrogen, hydroxyl, protected hydroxyl or OR^{ii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{ii} is an aliphatic or heteroaliphatic moiety, or wherein R_1 and R_5,

when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R_6 is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_7 is hydrogen, hydroxyl, protected hydroxyl, OR^{iii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{iii} is an aliphatic or heteroaliphatic moiety;

R_8 is hydrogen, hydroxyl, protected hydroxyl or OR^{iv},

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R_9 is hydrogen, $-CF_3$, -CHO, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R_{10} is hydroxyl or protected hydroxyl;

R_{11} and R_{12} are each independently hydrogen, hydroxyl or OR^v, or an aliphatic or heteroaliphatic moiety, or, when taken together, may be –(C=O)-;

wherein R^v is an aliphatic or heteroaliphatic moiety;

and R_{13} and R_{14} are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety; and

pharmaceutically acceptable derivatives thereof;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or ~~unsubstitued~~ unsubstituted;

with the proviso that when R_4, R_5, R_8 and R_{10} are each hydroxyl, R_7 is hydrogen, R_{13} and R_{14} are each methyl, R_2 and R_3, taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

(i) R_1 is methyl, R_9 is hydrogen, (R_{11}, R_{12}) is (=O) and R_6 is ethyl or isopropyl;

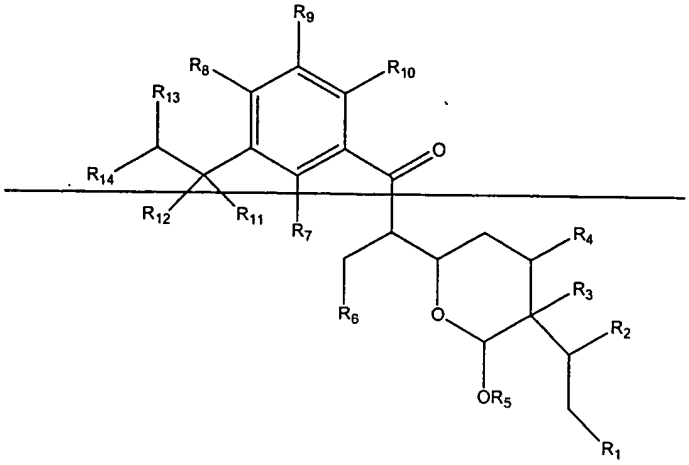
(ii) R_1 is methyl, R_9 is CHO, (R_{11}, R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;

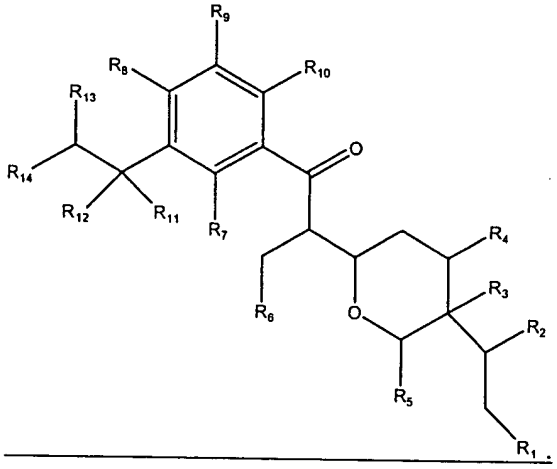
(ii) R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;

(iv) R_1 is methyl, R_9 is $COCH_3$, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and

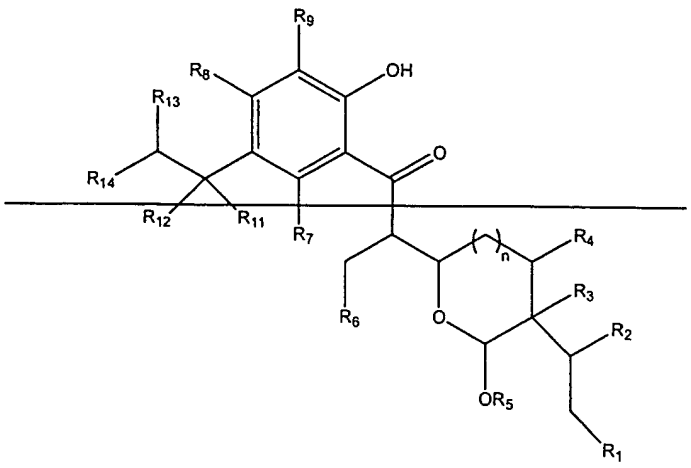
(v) R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl.

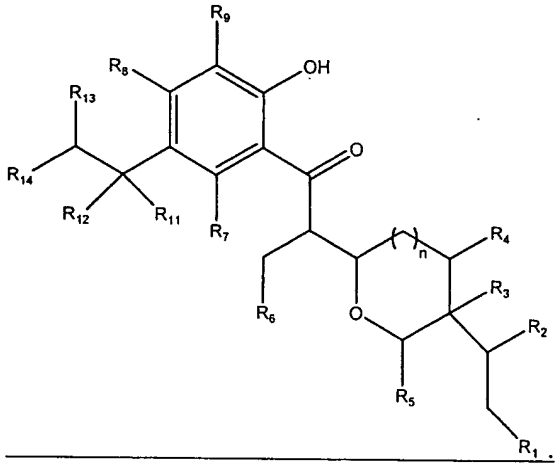
23. The pharmaceutical composition of claim 22 wherein n is 1 and the compound has the structure:



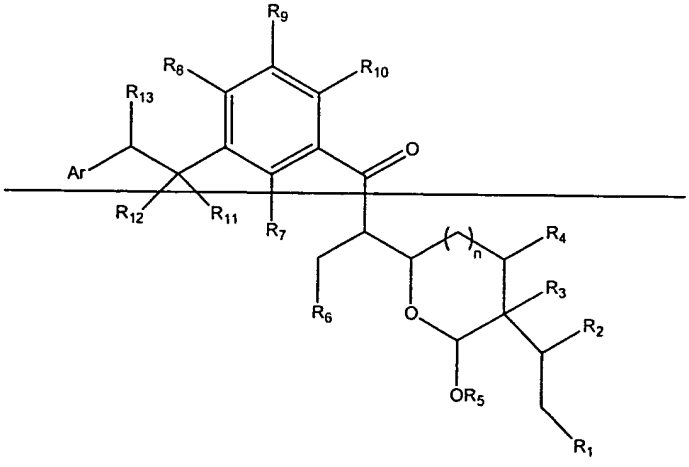


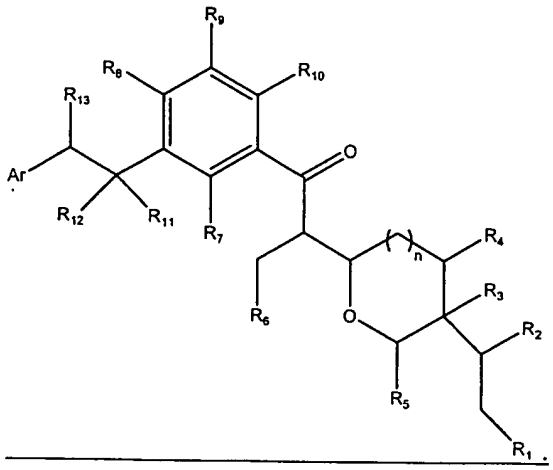
24. The pharmaceutical composition of claim 22 wherein R_{10} is hydroxyl and the compound has the structure:



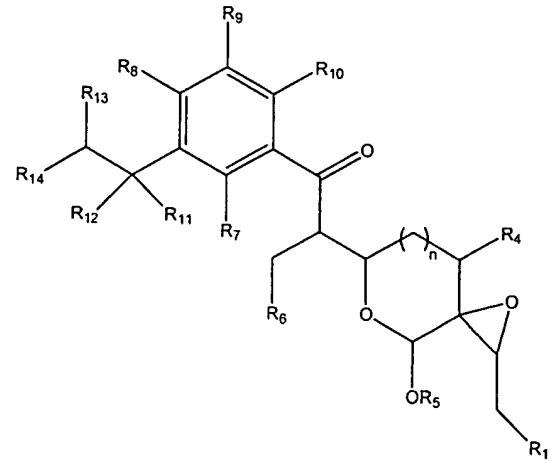


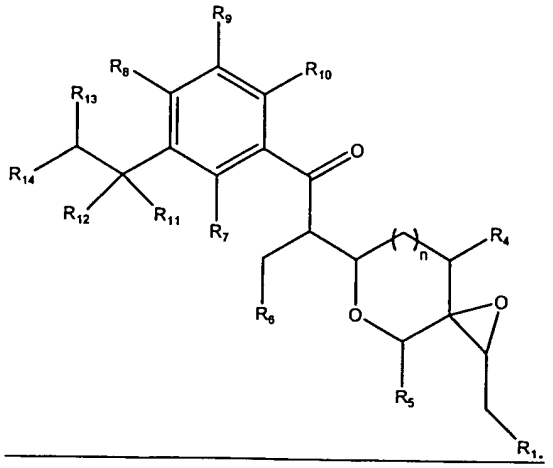
25. The pharmaceutical composition of claim 22 wherein R_{14} is aryl and the compound has the structure:





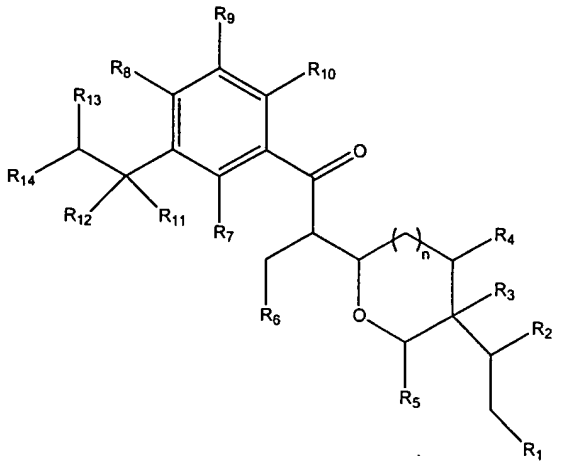
26. The pharmaceutical composition of claim 22 wherein R_2 and R_3, taken together, form an epoxide, and the compound has the structure:





43. A method for treating cancer comprising:

administering to a subject in need thereof a therapeutically effective amount of a compound having the structure:



~~and~~ or pharmaceutically acceptable ~~derivatives~~ derivative thereof;

wherein n is 0, 1 or 2;

R_1 is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_2 and R_3 are each independently hydrogen, or, when taken together, may be –O- or –$(CH_2)_q$- , where q is 1, 2 or 3;

R_4 is hydrogen, hydroxyl, protected hydroxyl or OR^i, or an aliphatic or heteroaliphatic moiety,

wherein R^i is an aliphatic or heteroaliphatic moiety;

R_5 is hydrogen, hydroxyl, protected hydroxyl or OR^{ii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{ii} is an aliphatic or heteroaliphatic moiety, or wherein R_1 and R_5, when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R_6 is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_7 is hydrogen, hydroxyl, protected hydroxyl, OR^{iii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{iii} is an aliphatic or heteroaliphatic moiety;

R_8 is hydrogen, hydroxyl, protected hydroxyl or OR^{iv},

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R_9 is hydrogen, $-CF_3$, -CHO, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R_{10} is hydroxyl or protected hydroxyl;

R_{11} and R_{12} are each independently hydrogen, hydroxyl or OR^v, or an aliphatic or heteroaliphatic moiety, or, when taken together, may be –(C=O)-;

wherein R^v is an aliphatic or heteroaliphatic moiety;

and R_{13} and R_{14} are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or ~~unsubstitued.~~ unsubstitued;

with the proviso that when R_4, R_5, R_8 and R_{10} are each hydroxyl, R_7 is hydrogen, R_{13} and R_{14} are each methyl, R_2 and R_3, taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

(i) R_1 is methyl, R_9 is hydrogen, (R_{11}, R_{12}) is (=O) and R_6 is ethyl or isopropyl;

(ii) R_1 is methyl, R_9 is CHO, (R_{11}, R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;

(ii) R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;

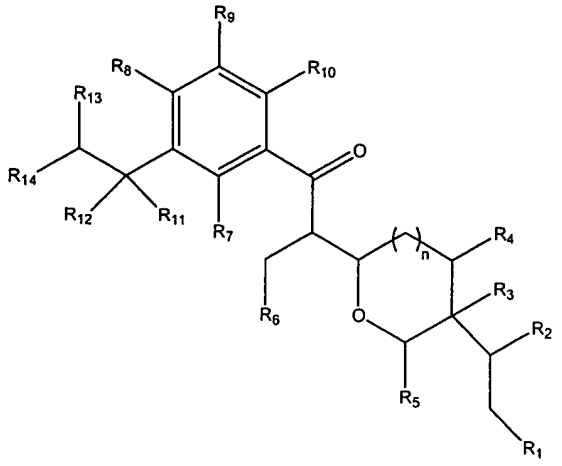
(iv) R_1 is methyl, R_9 is $COCH_3$, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and

(v) R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl.

SUBSTITUTE SHEETS

Claims

1. A compound having the structure:



or pharmaceutically acceptable derivative thereof;

wherein n is 0, 1 or 2;

R_1 is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_2 and R_3 are each independently hydrogen, or, when taken together, may be –O- or –$(CH_2)_q$- , wherein q is 1, 2 or 3;

R_4 is hydrogen, hydroxyl, protected hydroxyl or OR^i, or an aliphatic or heteroaliphatic moiety,

wherein R^i is an aliphatic or heteroaliphatic moiety;

R_5 is hydrogen, hydroxyl, protected hydroxyl or OR^{ii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{ii} is an aliphatic or heteroaliphatic moiety, or wherein R_1 and R_5, when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R_6 is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_7 is hydrogen, hydroxyl, protected hydroxyl, OR^{iii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{iii} is an aliphatic or heteroaliphatic moiety;

R_8 is hydrogen, hydroxyl, protected hydroxyl or OR^{iv},

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R_9 is hydrogen, $-CF_3$, -CHO, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R_{10} is hydroxyl or protected hydroxyl;

R_{11} and R_{12} are each independently hydrogen, hydroxyl or OR^v, or an aliphatic or heteroaliphatic moiety, or, when taken together, may be –(C=O)-;

wherein R^v is an aliphatic or heteroaliphatic moiety;

and R_{13} and R_{14} are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or unsubstituted;

with the proviso that:

(a) when R_4, R_5, R_8 and R_{10} are each hydroxyl, R_7 is hydrogen, R_{13} and R_{14} are each methyl, R_2 and R_3, taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

(i) R_1 is methyl, R_9 is hydrogen, (R_{11}, R_{12}) is (=O) and R_6 is ethyl or isopropyl;

(ii) R_1 is methyl, R_9 is CHO, (R_{11}, R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;

(iii) R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;

(iv) R_1 is methyl, R_9 is $COCH_3$, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and

(v) R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and

(b) when R_1 is methyl, R_2 and R_3, taken together, form an epoxide, R_6 is ethyl, R_7 is hydrogen, (R_{11}, R_{12}) is (OMe, H), R_{13} and R_{14} are each methyl and n is 1, the following groups do not occur simultaneously as defined: R_4 and R_5 is OH or OBn, R_8 and R_{10} is OH or $-OCH_2OCH_3$ and R_9 is –CHO, $-CH_2OH$ or $-CH_2OTBS$.

2. The compound of claim 1 wherein n is 1 and the compound has the structure:

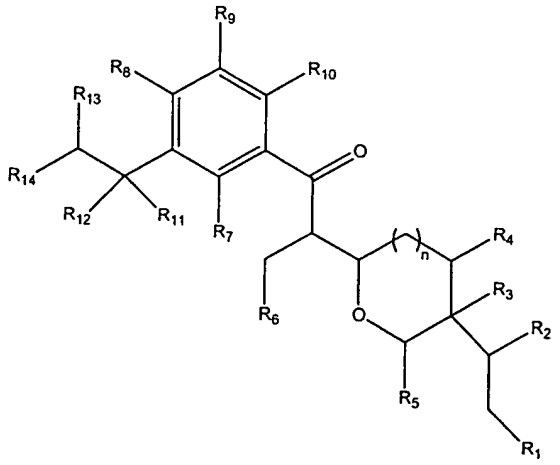
substituted or unsubstituted, branched or unbranched or cyclic or acyclic, and wherein the aryl substitutent may be substituted or unsubstituted.

20. The compound of claim 4 or 7 wherein R_{13} is lower alkyl, and wherein the alkyl substitutent may be substituted or unsubstituted, linear or branched or cyclic or acyclic.

21. The compound of claim 7 wherein R_1 is hydrogen or lower alkyl, R_5 is hydroxyl or lower alkoxyl, R_6 is lower alkyl, R_7 is hydrogen, hydroxyl, lower alkyl or lower alkoxyl, R_8 is hydrogen, hydroxyl or protected hydroxyl, R_9 is –CHO or $-CH_2OR^{vi}$, R_{11} and R_{12} are independently hydrogen or lower alkoxyl, and R_{13} is lower alkyl; wherein R^{vi} is hydrogen, protecting group or an aliphatic or heteroaliphatic moiety;

whereby each of the foregoing alkyl, alkoxyl, aliphatic and heteroaliphatic moieties may be independently substituted or unsubstituted, linear or branched, or cyclic or acyclic.

22. A pharmaceutical composition comprising:
a compound having the structure:



or pharmaceutically acceptable derivative thereof; and
a pharmaceutically acceptable carrier;
wherein n is 0, 1 or 2;
R_1 is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_2 and R_3 are each independently hydrogen, or, when taken together, may be –O- or –$(CH_2)_q$- , where q is 1, 2 or 3;

R_4 is hydrogen, hydroxyl, protected hydroxyl or OR^i, or an aliphatic or heteroaliphatic moiety,

wherein R^i is an aliphatic or heteroaliphatic moiety;

R_5 is hydrogen, hydroxyl, protected hydroxyl or OR^{ii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{ii} is an aliphatic or heteroaliphatic moiety, or wherein R_1 and R_5, when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R_6 is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_7 is hydrogen, hydroxyl, protected hydroxyl, OR^{iii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{iii} is an aliphatic or heteroaliphatic moiety;

R_8 is hydrogen, hydroxyl, protected hydroxyl or OR^{iv},

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R_9 is hydrogen, -CF_3, -CHO, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R_{10} is hydroxyl or protected hydroxyl;

R_{11} and R_{12} are each independently hydrogen, hydroxyl or OR^v, or an aliphatic or heteroaliphatic moiety, or, when taken together, may be –(C=O)-;

wherein R^v is an aliphatic or heteroaliphatic moiety;

and R_{13} and R_{14} are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety; and

pharmaceutically acceptable derivatives thereof;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or unsubstituted;

with the proviso that when R_4, R_5, R_8 and R_{10} are each hydroxyl, R_7 is hydrogen, R_{13} and R_{14} are each methyl, R_2 and R_3, taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

(i) R_1 is methyl, R_9 is hydrogen, (R_{11}, R_{12}) is (=O) and R_6 is ethyl or isopropyl;

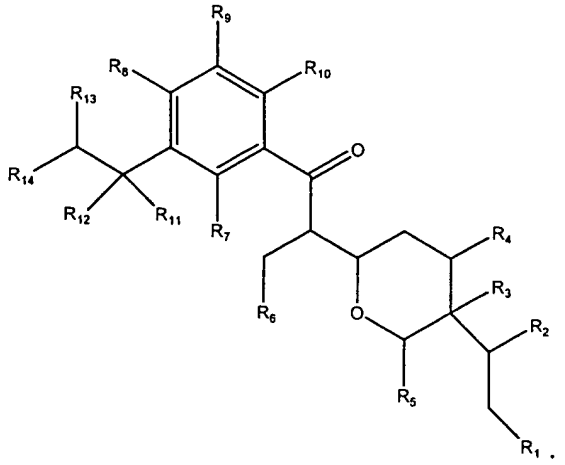
(ii) R_1 is methyl, R_9 is CHO, (R_{11}, R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;

(iii) R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;

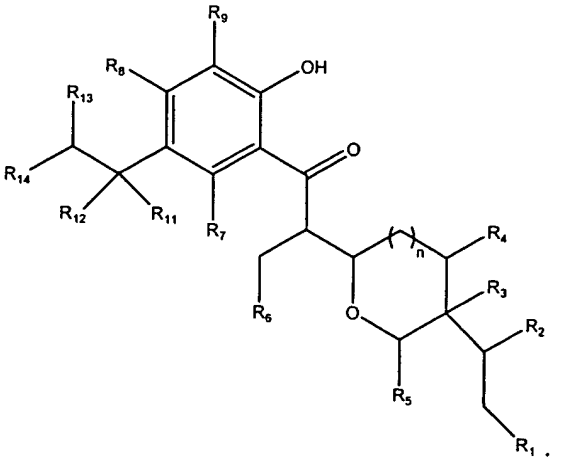
(iv) R_1 is methyl, R_9 is $COCH_3$, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and

(v) R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl.

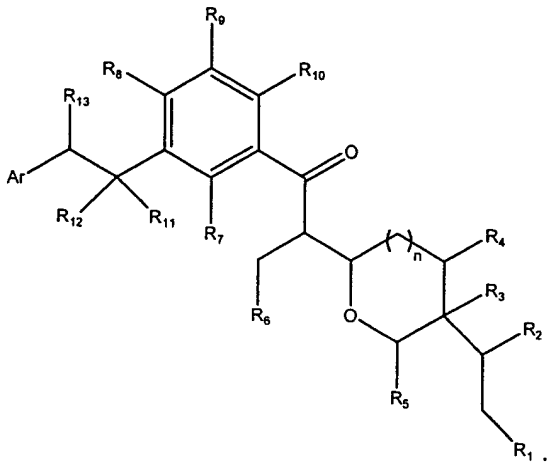
23. The pharmaceutical composition of claim 22 wherein n is 1 and the compound has the structure:



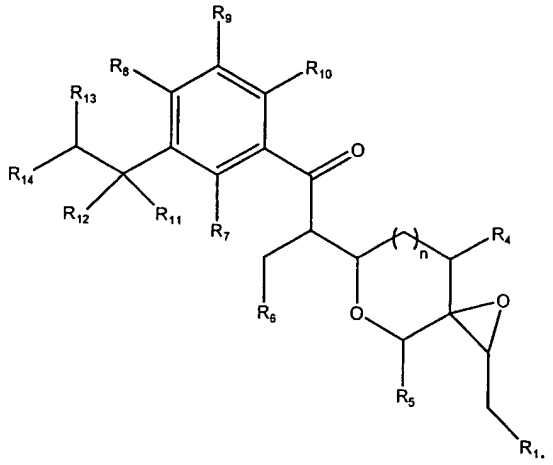
24. The pharmaceutical composition of claim 22 wherein R_{10} is hydroxyl and the compound has the structure:



25. The pharmaceutical composition of claim 22 wherein R_{14} is aryl and the compound has the structure:



26. The pharmaceutical composition of claim 22 wherein R_2 and R_3, taken together, form an epoxide, and the compound has the structure:



27. The pharmaceutical composition of claim 22 wherein R_4 is hydroxyl and the compound has the structure:

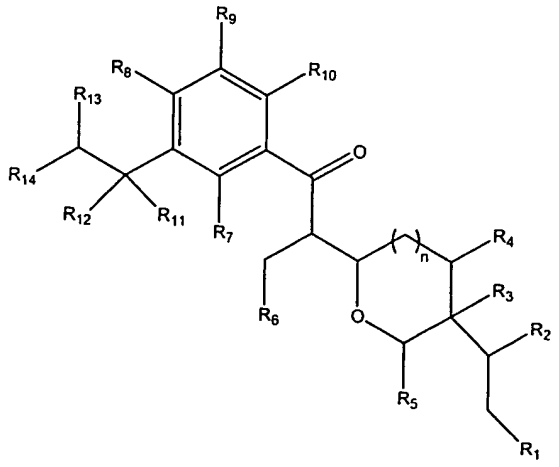
40. The pharmaceutical composition of any one of claims 22, 23, 24, 26 or 27 wherein R_{13} and R_{14} are independently hydrogen, lower alkyl or aryl, wherein the alkyl substitutent may be substituted or unsubstituted, branched or unbranched or cyclic or acyclic, and wherein the aryl substitutent may be substituted or unsubstituted.

41. The pharmaceutical composition of claim 25 or 28 wherein R_{13} is lower alkyl, and wherein the alkyl substitutent may be substituted or unsubstituted, linear or branched or cyclic or acyclic.

42. The pharmaceutical composition of claim 28 wherein R_1 is hydrogen or lower alkyl, R_5 is hydroxyl or lower alkoxyl, R_6 is lower alkyl, R_7 is hydrogen, hydroxyl, lower alkyl or lower alkoxyl, R_8 is hydrogen, hydroxyl or protected hydroxyl, R_9 is –CHO or $-CH_2OR^{vi}$, R_{11} and R_{12} are independently hydrogen or lower alkoxyl, and R_{13} is lower alkyl; wherein R^{vi} is hydrogen, protecting group or an aliphatic or heteroaliphatic moiety;

whereby each of the foregoing alkyl, alkoxyl, aliphatic and heteroaliphatic moieties may be independently substituted or unsubstituted, linear or branched, or cyclic or acyclic.

43. A method for treating cancer comprising:
administering to a subject in need thereof a therapeutically effective amount of a compound having the structure:



or pharmaceutically acceptable derivative thereof;

wherein n is 0, 1 or 2;

R_1 is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_2 and R_3 are each independently hydrogen, or, when taken together, may be –O- or –$(CH_2)_q$- , where q is 1, 2 or 3;

R_4 is hydrogen, hydroxyl, protected hydroxyl or OR^i, or an aliphatic or heteroaliphatic moiety,

wherein R^i is an aliphatic or heteroaliphatic moiety;

R_5 is hydrogen, hydroxyl, protected hydroxyl or OR^{ii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{ii} is an aliphatic or heteroaliphatic moiety, or wherein R_1 and R_5, when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R_6 is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_7 is hydrogen, hydroxyl, protected hydroxyl, OR^{iii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{iii} is an aliphatic or heteroaliphatic moiety;

R_8 is hydrogen, hydroxyl, protected hydroxyl or OR^{iv},

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R_9 is hydrogen, -CF_3, -CHO, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R_{10} is hydroxyl or protected hydroxyl;

R_{11} and R_{12} are each independently hydrogen, hydroxyl or OR^v, or an aliphatic or heteroaliphatic moiety, or, when taken together, may be –(C=O)-;

wherein R^v is an aliphatic or heteroaliphatic moiety;

and R_{13} and R_{14} are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or unsubstituted;

with the proviso that when R_4, R_5, R_8 and R_{10} are each hydroxyl, R_7 is hydrogen, R_{13} and R_{14} are each methyl, R_2 and R_3, taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

(i) R_1 is methyl, R_9 is hydrogen, (R_{11}, R_{12}) is (=O) and R_6 is ethyl or isopropyl;

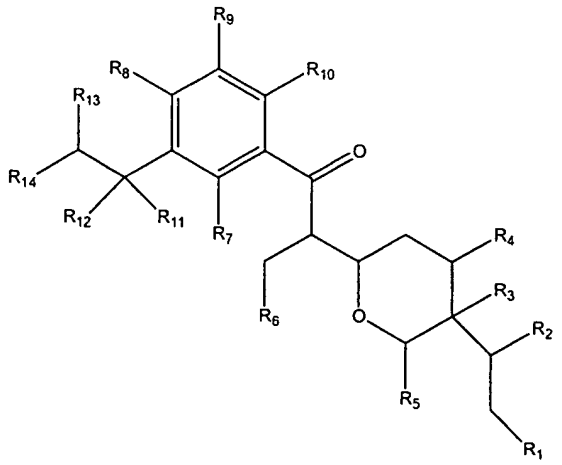
(ii) R_1 is methyl, R_9 is CHO, (R_{11}, R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;

(iii) R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;

(iv) R_1 is methyl, R_9 is $COCH_3$, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and

(v) R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl.

45. The method of claim 43 wherein in the compound n is 1 and the compound has the structure:



46. The method of claim 43 wherein in the compound R_{10} is hydroxyl and the compound has the structure: